Leadership in Vaccine Safety

Another vitally important aspect of immunization concerns vaccine safety. As a part of its mission, NIP works to ensure that vaccines are inherently safe and are delivered, handled, and administered in ways that ensure the quality and safety of the vaccines. Immunization surveillance, research, and education activities reduce risks associated with vaccines and help assure the appropriate, effective use of vaccines.

Continuing Activities in Vaccine Safety

Vaccine safety activities are an essential component of the National Immunization Program (NIP) mission to prevent disease, disability, and death. Vaccines, which do so much to minimize the burden of disease, must not be a source of health problems. To continue to ensure the safety of vaccines, NIP works to

- Increase knowledge of genetic risk factors for vaccine reactions
- Use information in immunization registries to enhance vaccine safety efforts
- Increase opportunities for research studies on vaccine risks by qualified external organizations and researchers
- Improve vaccine benefit-risk communication, including parent and healthcare professional education, through expanded research and partnerships

Efforts to Assure Vaccine Safety

As a leader in immunization safety research and surveillance, CDC plays a vital role in assuring vaccine safety. Sound immunization policies and recommendations affecting the health of our nation depend upon continuous monitoring of vaccines and ongoing assessment of immunization benefits and risks. Serious adverse events after vaccination occur but are generally rare. Even with well-designed large pre-licensure clinical trials, it is difficult to detect rare adverse events. Therefore, post-marketing monitoring of adverse events after vaccination is essential. Using a multi-faceted approach, CDC's vaccine safety system identifies possible vaccine side effects, conducts epidemiological studies to determine whether a particular adverse event is caused by a specific vaccine, helps determine the appropriate public health response to vaccine safety concerns, evaluates public and healthcare provider perceptions of vaccination, and communicates the benefits and risks of vaccines to the public, media, and healthcare communities.

The Vaccine Identification Standards Initiative (VISI)

The Vaccine Identification Standards Initiative (VISI), a cooperative effort by NIP and partners in the vaccine and immunization system, aims to establish uniform standards for vaccine packaging, labeling, and recording. Its goal is to reduce the risk of medical errors and make it easier to accurately transfer immunization information into medical records and immunization registries. Improved recordkeeping helps researchers monitor adverse reactions following vaccination and track vaccine lots for safety surveillance.

VISI guidelines include bar-coded peel-off stickers on vaccine vials and pre-filled syringes as well as standardized requirements for information in carton sidebars. On April 26, 2004, the Food and Drug Administration (FDA) began to require bar codes on all new unit-of-use packaging of drugs, including vaccines—an important first step towards fulfilling VISI recommendations. By April 26, 2006, such bar coding must be applied to all existing products.

Vaccine Acceptance and Risk Perception Activities

The Vaccine Acceptance and Risk Perception Team conducts ongoing research to

- Better understand how individuals interpret risks and make vaccination decisions
- Determine how best to communicate with different groups of people about the need for vaccination and the risks and benefits of vaccines
- Develop and evaluate interventions that help individuals make informed decisions about vaccinations

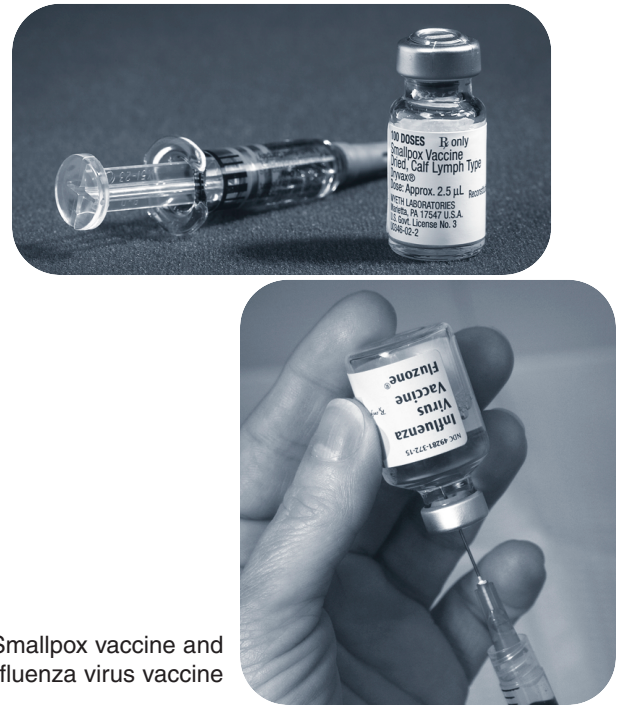
Research is under way to address each of these goals. In 2004, an international study in collaboration with the World Health Organization was initiated to better understand the vaccine safety perceptions of parents in developing countries. Also in 2004, a new initiative for communicating with parents about childhood immunizations, Make it REAL, was instituted. An increasing number of parents and healthcare providers have little or no personal experience with or knowledge of many of the diseases that childhood immunizations prevent. Parents in particular may not perceive the need for many currently recommended childhood vaccines. Parents need and want to know the importance of vaccination and to understand its risks and benefits. This new initiative shifts education and communication efforts from a strategy of "make it obligatory" to a campaign to "make it real," to help parents understand the true need for vaccines and the real consequences of not vaccinating. This initiative reflects the commitment to make parents partners in vaccine decisions and active participants in the health of their children and the public health of the community.

CDC's Anthrax Vaccine (AVA) Human Clinical Trial

In collaboration with National Center for Infectious Disease (NCID), NIP has recently completed the interim safety analysis of the Anthrax Vaccine (AVA) Human Clinical Trial. The results of the interim analysis were presented to the Food and Drug Administration in January 2005. The primary objectives of the interim analysis are to evaluate the feasibility of changing the route of administration (subcutaneous to intramuscular) and to simplify the vaccination schedule by dropping the two-week priming dose. The trial continues, and a complete analysis is planned for 2007. This analysis will assess the feasibility of further simplifying the priming regimen by dropping additional vaccine doses and will present the results of parallel non-human-primate challenge studies that can provide valuable insight into the immunologic correlates of protection.

Smallpox Vaccine Safety Workgroup (SVS WG) Completes Its Mission

This joint working group of the Advisory Committee on Immunization Practices (ACIP) and the Armed Forces Epidemiological Board (AFEB) met in 2003 and 2004 to provide safety oversight for the smallpox vaccination programs. The group concluded that preventable adverse events had been reduced through education, screening, and attention to vaccination site management, although exposure of pregnant women to smallpox vaccine was not eliminated.



Smallpox vaccine and Influenza virus vaccine

Parents should be partners in vaccine decisions and active participants in the health of their children and the public health of the community.

Vaccine Analytic Unit (VAU)

The Vaccine Analytic Unit (VAU) is a vaccine safety research collaboration of CDC, the Department of Defense (DoD), and FDA. VAU staff conduct vaccine post-marketing surveillance investigations using data collected by the Defense Medical Surveillance System (DMSS), which holds information on vaccinations, hospitalizations, outpatient visits, occupational variables, and demographics for all U.S. military personnel. These investigations evaluate potential relationships between biodefense vaccines, including anthrax vaccine adsorbed (AVA), and adverse health events in the military.

In 2004, VAU collaborators and a workgroup of the National Vaccine Advisory Committee approved VAU's research agenda of priority adverse events potentially related to AVA. This approval followed a thorough review and a detailed process for setting priorities (a report on this process has been cleared by CDC for publication). An independent, comprehensive surveillance system assessment report was produced to guide future VAU epidemiological work using the DMSS. Necessary contracts were secured for medical chart review abstractions, contractor hiring, and software procurement. Cross-CDC coordination and high-level DoD sponsorship of relevant investigations was negotiated to provide appropriate expertise and approvals.

The first research protocols have been drafted and approved by CDC Institutional Review Board (IRB) and collaborators. VAU is now engaged in several vaccine safety investigations, including those that study possible relationships between AVA and optic neuritis, and AVA and systemic lupus erythematosus. VAU is also investigating health events following multiple, near-simultaneous vaccinations in the military. In 2004 VAU also assisted the FDA in fulfilling a Data Safety Monitoring Board (DSMB) request to calculate pericarditis-vaccinia risks for the U.S. military. These anthrax vaccine safety trials will enhance the safety knowledge and acceptability of the anthrax vaccine in the U.S. military.

Anthrax Vaccination Program and Related Research Studies

As of December 2, 2004, 1093 persons had received at least one dose of anthrax vaccine through the Anthrax Vaccination Program (AVP). This program, the result of collaboration between NIP and the National Center for Infectious Diseases, began in June 2002. The program offers pre-exposure anthrax vaccine to groups at risk for repeated exposures to B. anthracis spores. These groups include laboratory personnel handling environmental specimens (especially powders) and performing confirmatory testing for B. anthracis in the U.S. Laboratory Response Network for Bioterrorism Level B laboratories or above; workers who will make repeated entries into known B. anthracis spore-contaminated areas after a terrorist attack; and workers in other settings in which repeated exposure to aerosolized B. anthracis spores might occur. NIP has also designed and implemented these research studies in association with AVP:

- "Survey of Persons Eligible to Participate in the Anthrax Vaccination Program," to determine how people make the decision to accept or decline the anthrax vaccine
- "Comparative Evaluation of the Effect of Anthrax Vaccine Adsorbed on Health Related Quality of Life-Comparing Vaccinated to Unvaccinated Workers"
- "Evaluation of the Effects of Hormonal Phase on the Occurrence of Local Adverse Events Following Immunization with Anthrax Vaccine in Women"

Enrollment in these studies will continue in 2005, and results are expected in early 2006.

The National Vaccine Health Care Center Network

Established in 2002, the centers are responsible for follow-up and case management for military personnel who experienced adverse reactions following anthrax vaccination. The knowledge gained from the research and clinical efforts of the vaccine healthcare centers (VHCs) will be used to improve the safety and quality of future vaccinations and to increase military personnel's confidence in the safety of DoD-required vaccines. In addition, VHCs are expected to improve reporting of vaccine-associated adverse events and facilitate further research into adverse events that may be related to vaccination.

Knowledge, Attitudes and Beliefs (KAB) Survey of Military Vaccine Providers

NIP is collaborating with the Walter Reed Army Medical Center VHC Network to develop a survey to assess the knowledge, attitudes, and beliefs of military healthcare providers about reporting adverse events following anthrax and other immunizations to VAERS. Findings of this survey will be used to inform a comparison survey of civilian healthcare providers, to develop more effective educational tools for VAERS, and ultimately to improve the quality of VAERS reporting.

Significant Events in Vaccine Safety in 2004

Institute of Medicine Immunization Safety Reviews

In the fall of 2000, CDC and the National Institutes of Health (NIH) requested that the National Academy of Sciences' Institute of Medicine (IOM) convene an Immunization Safety Review Committee. This independent expert committee was charged with examining hypotheses about existing and emerging immunization safety concerns each year through 2003. During 2004, the committee held its final meeting regarding MMR vaccine and autism and thimerosal-containing vaccines and autism. The report supports the safety of these vaccines by finding no association between these vaccines and the development of autism.

Working to Ensure Vaccine Safety: The Brighton Collaboration

The Brighton Collaboration was formed in fall 2000 to develop case definitions for adverse events following vaccination. The Collaboration has an international membership of more than 535 volunteer participants from 59 countries, with backgrounds in patient care, academic research, public health, vaccine clinical trials, and regulatory or manufacturing issues. In 2004, the Collaboration developed and published in the journal *Vaccine* six case definitions for adverse events that particularly concern parents, including definitions for persistent crying, fever, hypotonic-hyporesponsive episode, intussusception, nodule at injection site, and seizure.

Selected Vaccine Safety Studies in 2004

An Analysis of Rotavirus Vaccine Reports to the Vaccine Adverse Event Reporting System: More than Intussusception Alone? Pediatrics 2004: 113; e353.

This article presents a comprehensive safety summary for the first licensed rotavirus vaccine, demonstrating the range of gastrointestinal side effects (other than intussusception) that may have occurred. This information will assist clinical researchers and vaccine manufacturers in the development of a new and safer rotavirus vaccine, which remains an urgent public health need.

Lack of Association Between Hepatitis B Birth Immunization and Neonatal Death: A Population-Based Study from the Vaccine Safety Datalink Project. Pediatric Infectious Disease Journal, 2004; 23: 656–662.

Vaccine Safety Datalink (VSD) conducted the largest population-based study to assess the potential association between neonatal death and newborn immunization with hepatitis B vaccine (HBV). Using the birth cohort from 2 VSD sites, this study ascertained all deaths occurring under 29 days of age. The proportions of deaths among birth HBV-vaccinated and unvaccinated newborns were compared and reviewed for the causes and circumstances of death. Detailed clinical reviews were performed for all HBV-vaccinated neonates who died as well as for a sample of unvaccinated neonates who died. In addition, causes of death were categorized as either expected or unexpected. Results from this study concluded there was no increase in mortality caused by HBV use among infants.

Safety of the Trivalent Inactivated Influenza Vaccine Among Children: A Population-Based Study. Archives of Pediatrics and Adolescent Medicine, 2004; 158: 1031–1036

The trivalent inactivated influenza vaccine (flu shot) is thought to be safe for children. The most common events reported to the Vaccine Adverse Event Reporting System (VAERS) include fever, asthma, convulsions, and dyspnea (breathing difficulty). Despite the wide use of this vaccine, there are actually no published studies evaluating its safety in a large population of children. Vaccine Safety Datalink (VSD) was used to screen a large population of children who had received the vaccine for evidence of increased risk of medically attended events during the two weeks following vaccination. In this screening analysis, children vaccinated from 1993–1999 were randomly divided into two equal groups. In group A, the risks of outpatient, emergency department, and inpatient visits during the 14 days following vaccination were compared to the risks of visits in two control periods. Significant plausible medically attended events identified in group A were then analyzed in group B, using the same control periods. Medically attended events significant in both groups were considered potentially associated with vaccination and were assessed by chart review. Results from this study did not reveal any evidence of important medically attended events associated with pediatric influenza vaccination.

Infant Vaccinations and Childhood Asthma Among Full-Term Infants. Pharmacoepidemiology & Drug Safety, 2004; 13: 1–9

This study was conducted to determine whether infant vaccinations are associated with childhood asthma among full-term infants and to describe the relationships between characteristics of infant wheezing and childhood asthma. Baseline data from a study of infant wheezing were used to select full-term infants born into a VSD health maintenance organization (HMO) during 1991–1994. Information was abstracted for infancy regarding wheezing, vaccinations, and asthma risk factors. Using automated data, asthma cases in 1998 among those enrolled for at least 6 months in the HMO were identified. A total of 1778 full-term infants met the study criterion, and among those 9% had asthma in 1998. Childhood asthma was not significantly associated with having received hepatitis B vaccine or with age at first hepatitis B vaccination. It was also not significantly associated with the number of whole-cell pertussis, Haemophilus influenzae type b, or oral polio vaccine doses, receipt of MMR vaccine, or the total number of vaccine doses combined. In this study, childhood asthma was significantly associated only with the number of wheezing episodes.

Under-immunization in Children: Impact of Vaccine Safety Concerns on Immunization Status. Pediatrics 2004; 114: e16–22

It has been suggested that some parents do not immunize their children because of concerns about vaccines. A study compared the attitudes, beliefs, and behaviors of parents of children who are under-immunized for two or more vaccines and who have recently received negative medical attention with those of parents of children fully immunized for recommended vaccines. Among cases studied, 14.8% of under-immunization was attributable to parental attitudes, beliefs, and behaviors. Although concerns were significantly more common among parents of under-immunized children, many parents of fully immunized children shared similar attitudes, beliefs, and behaviors, suggesting a risk to current high vaccination levels. The study shows that, for both groups, attitudes, beliefs, and behaviors that indicate vaccine safety concerns contribute substantially to under-immunization in the United States.

Vaccine Policy Changes and Epidemiology of Poliomyelitis in the United States. Journal of the American Medical Association, 2004; 292(14), 1696–1701

This study examined national surveillance data from 1990 through 2003 for cases of confirmed paralytic poliomyelitis. The study found that 13 cases of paralytic poliomyelitis that occurred during the period 1997–1999 were associated with the all-oral polio vaccine schedule; no cases occurred with the inactive polio vaccine-oral polio (IPV-OPV) vaccine schedule. After the U.S. implemented its all-IPV schedule, no paralytic polio cases occurred. The change in polio vaccination policy from OPV to exclusive use of IPV was successfully implemented, and this change led to the elimination of vaccine-associated paralytic polio in the United States.

Success Story

The Vaccine Adverse Event Reporting System (VAERS)

The Vaccine Adverse Event Reporting System (VAERS), a program for vaccine safety monitoring jointly administered by CDC and the Food and Drug Administration (FDA), works like an "early warning" system. VAERS accepts reports from vaccine recipients, parents and guardians, healthcare providers, and all others for any suspected adverse event following immunization, even if there is no proof that the event was caused by a vaccine. A cornerstone of vaccine safety monitoring, VAERS supports the collection, review, and analysis of spontaneously reported adverse events. CDC and FDA have published and presented many vaccine safety studies based on VAERS data.

During 2004, the VAERS system was evaluated, enhanced, and expanded, and the contract renewed for an additional seven years. This year, VAERS reports identified vaccine administration errors involving mix-ups between tetanus toxoids-containing vaccines and TB skin tests (*MMWR* 7/30/04). Results from these findings are being used in education and outreach activities with healthcare providers. VAERS reports also documented a decreasing trend in reports about influenza vaccine and Guillain-Barré syndrome (a rare but serious neurological disorder linked to the 1976 swine flu vaccine). This finding was reassuring, especially in light of the increasing coverage of influenza vaccine in the general population.

The VAERS program continued its work with the National Smallpox Immunization Program to monitor smallpox vaccine adverse events for both civilian and military populations. VAERS monitoring helped identify myopericarditis following vaccination and led to changes in information and educational materials for smallpox vaccines. VAERS enhancements in response to preparation for the smallpox program improved CDC's capacity to respond to mass immunization campaigns associated with vaccine-preventable disease threats. Online reporting service and VAERS information are available on the web at **www.vaers.org**.

VAERS also expanded partnerships and initiated a workgroup to explore linkages between VAERS and immunization registries. This partnership will facilitate VAERS reporting through registries, should provide data on the number of children receiving immunizations, and will improve interpretation of VAERS surveillance data.

A cornerstone of vaccine safety monitoring, VAERS supports the collection, review, and analysis of spontaneously reported adverse events.